Can the ice-water test predict the outcome of intradetrusor injections of botulinum toxin in patients with neurogenic bladder dysfunction?

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ORIGINAL ARTICLE

Can the ice-water test predict the outcome of intradetrusor injections of botulinum toxin in patients with neurogenic bladder dysfunction?

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Keywords Botulinum toxin type A · Neurogenic bladder · Outcome assessment (health care) · Urodynamics

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Introduction

In the last years several studies demonstrated that botulinum toxin A injection into the detrusor muscle is a safe and valuable treatment of neurogenic incontinence due to detrusor overactivity [1–3]. A dose of 300 international units is needed to counteract an overactive detrusor. Schurch et al. [1], showed a high rate of complete continence and satisfaction, a significant increase in reflex volume (RV) and maximum cystometric bladder capacity and a significant decrease in maximum detrusor voiding pressure in spinal cord injured patients with incontinence resistant to anticholinergic treatment. Recently, the safety and efficacy of the treatment have been confirmed in a randomized placebo-controlled study [4].

However, not all patients respond to the treatment; the duration of efficacy ranges considerably from 6 to 12 months, some patients become fully continent while others do not, and rarely do the patients become resistant after repeat injection. Reasons for a variable response are unknown and a test to predict the response to the treatment would be of value to distinguish between potential responders and nonresponders before injection.

In this study we evaluated urodynamic criteria before and after intradetrusor injections of botulinum toxin and hypothesized that the urodynamic ice-water test can be used as a predictive factor for the response to the treatment.

Methods

Patients

A total of 22 patients (13 women and 9 men, mean age of 42.5 years (range 15–70 years) who had received an

intradetrusor injection of botulinum toxin (300 units of Botox®) for treatment of neurogenic detrusor overactivity in our institution were included in this study. The neurogenic bladder dysfunction was due to paraplegia in ten cases, tetraplegia in four cases, multiple sclerosis in five cases and nontraumatic spinal lesions in three cases. Indications for injecting the detrusor muscle with botulinum toxin A were: neurogenic incontinence or side effects of anticholinergic medication, which led to the discontinuation of the therapy. Patients with serious concomitant illness and pregnant or breast-feeding women, were excluded. Seventeen patients were on clean intermittent catheterization and five on indwelling catheter (suprapubic or transurethral).

Urodynamic assessment and toxin injection

Complete urodynamic assessment was performed in every patient before and after the application of botulinum toxin type A according to the standards of the International Continence Society [5]. The ice-water test was carried out prior to the therapy. The follow-up examination was done on the maximum effect of botulinum toxin A with a mean after 3 months (range 1–8 months).

At the beginning of the urodynamic measurement baseline an ice-water test was performed. With the patient supine, water at 4°C was instilled as quickly as possible through a 12 Fr catheter at 100 ml/min, using a maximum volume of 200 ml. Instillation was stopped before the maximum volume when the patient showed a leakage or got autonomic dysreflexia. Bladder and urethral pressures were measured by a second microtransducer after correct placing under radiologic guidance. Intraabdominal pressure was recorded simultaneously intrarectally to exclude artefacts. The test was considered positive if a phasic detrusor contraction >30 cmH_2O was recorded or a fluid expulsion beside the catheter occurred. A detrusor pressure of 30 cmH_2O was taken as cutoff value, similar to that used by Geirsson et al. [6]. For the baseline and follow-up urodynamic assessments the following parameters were specially determined: maximum cystometric capacity (MCC), reflex volume (RV), maximum detrusor pressure during voiding (MVP) and bladder compliance (BC). Maximum cystometric capacity was defined as the volume at which involuntary voiding occurred or in the absence of involuntary voiding when the filling was stopped, usually done at 500 ml. Reflex volume corresponded to the infused volume at the start of the first reflex detrusor contraction during filling cystometry. Without involuntary voiding maximum detrusor pressure during voiding was assigned as the maximum pressure during the reflex detrusor contraction. Finally, BC was calculated as the change in volume divided by the change in detrusor pressure at MCC or immediately before the start of a reflex detrusor contraction that causes significant leakage.

A total dose of 300 units of botulinum toxin type A (Botox®, Allergan Inc.) were injected into the detrusor muscle under cystoscopic control. The total dose of 300 units was distributed over 30 injection sites in the bladder (10 units and 1 ml per site) sparing the trigone. A normal rigid 22 FF cystoscope and a flexible 7 FF injection needle were used.

Data analysis

The urodynamic parameters MCC, RV, MVP and BC after injection (at maximum effect) were compared to the baseline values. Statistical analysis was performed by paired *t* test, significance considered at $P < 0.05$. The urodynamic parameters after treatment were also divided by the corresponding parameter before treatment to calculate a quotient.

During the ice-water test maximum pressure rise and time to maximum pressure were measured. Maximum detrusor pressure during ice-water test was divided by the time to reach maximum detrusor pressure; this quotient (velocity of pressure rise) was taken as the degree of positivity of the test (Fig. 1). Correlations between the criteria of the ice-water test and quotients of the urodynamic parameters were evaluated by Spearmen's Rho coefficient calculation.

Results

All 22 patients have well tolerated the injection of botulinum toxin A, no complications or toxin related side effects were reported. At the follow-up examination only two patients reported no improvement of the incontinence, three reported a reduction of the incontinence episodes and all other patients were continent. Of the patients who took anticholinergic drugs before treatment, 13% could reduce

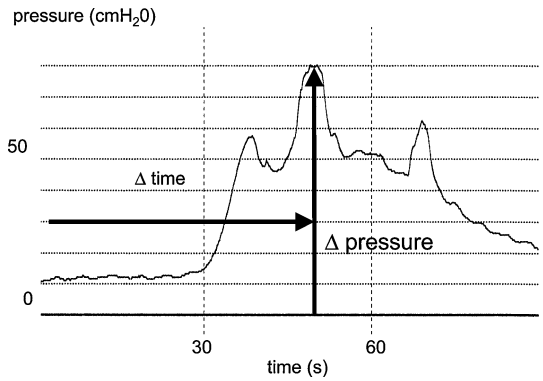

Fig. 1 Maximum pressure rise and time to maximum pressure during the ice-water test as a quotient determining the velocity of pressure, which was interpreted as the degree of positivity

the dose and 66% definitively withdrew from anticholinergic medication after the injection.

Urodynamic evaluation showed a significant increase in mean MCC from 259 ml to 332 ml ($P < 0.05$) and a significant increase in mean RV from 187 to 287 ml ($P < 0.001$). There was a significant decrease in mean MVP before and after treatment from 76 to 37 cmH_20 ($P < 0.01$). Mean BC increased markedly but not significantly from 36 to 73 ml/cmH_2O ($P = 0.22$). The mean calculated quotient (parameter after treatment divided by parameter before treatment) was 1.6, 2.0, 0.6 and 5.8 for MCC, RV, MVP and BC, respectively.

Mean maximum detrusor pressure during ice-water test was 98 cmH_2O (range 34–240), mean time to reach this maximum detrusor pressure amounted 97 s (range 42–210 s). The mean velocity of pressure rise of the ice-water test was 1.15 cmH_2O/s ranged from 0.23 to 3.

The increasing MCC after injection of botulinum toxin A showed a small positive, but insignificant correlation of 0.25 to the velocity of the ice-water test (Fig. 2). So did the change in RV with 0.2 (Fig. 3). We observed a small negative, but insignificant correlation between change of MVP (Fig. 4) and BC (Fig. 5) during voiding with −0.2 and −0.17, respectively.

Discussion

The ice-water test was first described by Bors and Blinn in 1957; they reported that rapid filling of the bladder with ice-water leads to an immediate detrusor contraction in patients with an upper motor neuron lesion. Patients with a lower motor neuron lesion and neurologically normal persons showed no detrusor response [7]. In the study on cats, Fall et al. [8] observed a spinal micturition reflex to cold water which is carried by type C unmyelinated fibres in contrast to the micturition reflex normally mediated from mechanoreceptors by afferent A delta fibres. By activation of the bladder-cooling reflex, elicited from cold receptors in the bladder wall, a positive ice-water test is considered as a primitive reflex, like the Babinski reflex. The reflex is present at birth and then suppressed during nerval growth under inhibitory control at approximately 4 years. Some authors recommend the routine use of the ice-water test in the urodynamic evaluation because a positive test indicates a neurological lesion and is always negative in normal subjects [9, 10].

In recent years the test was evaluated in several studies of neurogenic bladder dysfunction and the diagnostic value was extended. So in a study by Geirsson et al., a positive

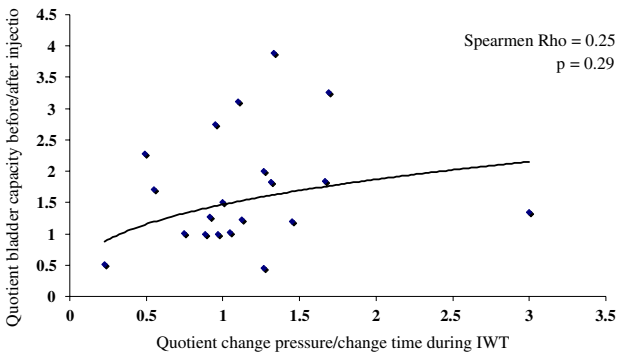

Fig. 2 Correlations between maximum bladder capacity before and after treatment and ice-water test criteria

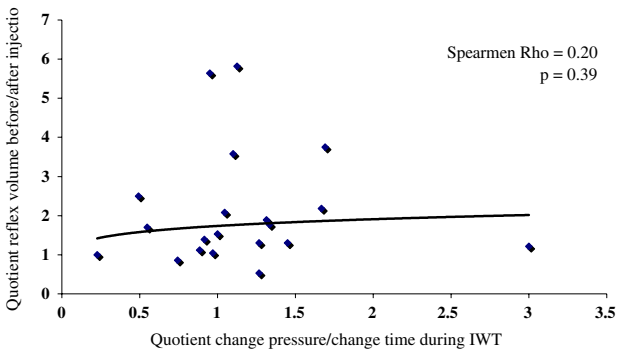

Fig. 3 Correlations between reflex volume before and after treatment and ice-water test criteria

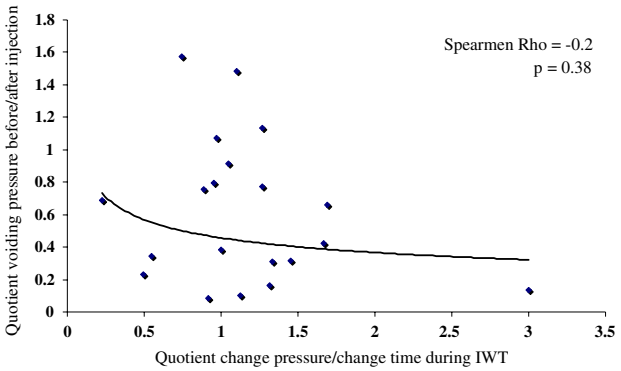

Fig. 4 Correlations between voiding pressure before and after treatment and ice-water test criteria

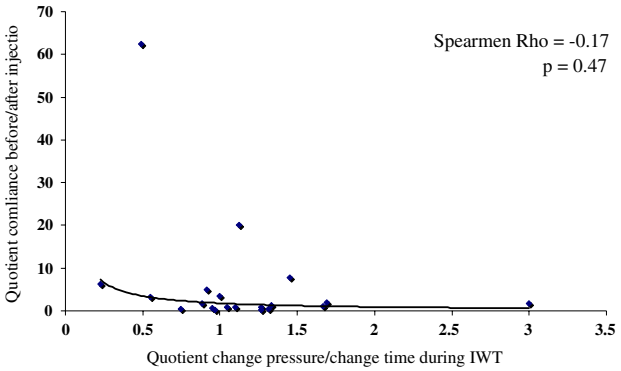

Fig. 5 Correlations between compliance before and after treatment and ice-water test criteria

response to the ice-water test was found in 93% of patients with central spinal lesions and in about 75% of the patients with overactive bladder associated with the three common neurological disorders multiple sclerosis, Parkinsonism and vascular-origin hemiplegia [11]. On the other hand, the test was always negative in patients with various disorders of micturition but no neurological lesions [10]. Moreover a positive ice-water test not only supports the diagnosis of a neurological disorder, it also has an important role of an early recognition of a neurological disease, especially in those patients with micturition disorders that are difficult to interpret [12]. In patients with multiple sclerosis a positive ice-water test can give strong evidence for spinal cord involvement, especially when it is associated with detrusor-sphincter dyssynergia [13]. That is the reason why we always perform an ice-water test as part of the first urodynamic assessment in our institution, particularly because it is simple to carry out.

Other studies focused on the incidence of a positive ice-water test in bladder outlet obstruction with controversial results. Chai et al. [14] reported a significantly higher incidence of a positive ice-water test compared to the unobstructed controls, Hirayama et al. [15] found similar results concerning bladder outlet obstruction. This observation could not be confirmed in another study of 16 patients with obstruction. Only one of these patients had a positive bladder-cooling test [16]. The above-mentioned assessments use different cutoff pressure values for a positive ice-water test. These conflicting results indicate the importance of a standardized performed test. For our data we considered the test to be positive when a detrusor contraction of >30 cmH_2O with or without fluid leakage was reported, as recommended by Geirsson et al. [6], based on the determination of the critical pressure in a large group of patients. In their work, Geirsson et al. [6] also showed that both the infusion speed and the infused volume were not decisive for the outcome of the test provided that the bladder was sufficiently cooled.

Most of the spinal cord injured, myelomeningocele and multiple sclerosis patients with neurogenic overactive bladder can be categorized as upper motor neuron dysfunction. Standard treatment options contain clean intermittent self-catheterization and oral anticholinergic drugs to achieve continence. These drugs have relevant side effects and may often not restore continence. Botulinum toxin injections into the detrusor were introduced in spinal cord injured patients in 1997 [1, 2]. The preliminary results showed that this therapeutic option could significantly improve subjective (satisfaction) and objective (urodynamic and degree of incontinence) parameters. In the recent years both retrospective studies with large patient numbers as well as prospective, randomized, placebo-controlled trials confirmed the preliminary data [3, 4]. The present study with 22 patients could also show a clear improvement of incontinence after injection of 300 units botulinum toxin A into the detrusor. So did the objective urodynamic parameters; we evaluated a significant increase in mean MCC and RV and a significant decrease in mean MVP. The data did not vary much compared to the previous studies.

Until now neither the severity of incontinence nor the objective urodynamic parameters could predict the effect of the intradetrusal injection of botulinum toxin although there is some evidence that the severity of detrusor overactivity and the method of voiding may have some bearing on treatment effect [17]. Usually, patients can be classified into responders and non-responders only after the intervention. Our study focused on the question if the efficacy of botulinum toxin A can be predicted based on an objective, standardized urodynamic test like the ice-water test. Geirsson [6], found a clear correlation between maximum detrusor pressure obtained by bladder cooling and maximum cystometric voiding pressure in patients with a positive but no correlation in those with a negative bladder cooling test. On the other hand in most studies concerning the ice-water test only the qualitative result of the test was taken into account [10, 13, 18] and compared to other factors. Besides the maximum detrusor pressure during ice-water test we evaluated additionally the time to reach this maximum pressure. The quotient of these two parameters was taken as the velocity of pressure rise representing the degree of positivity of the ice-water test. Although we could not detect clear correlations between the parameters of the pre-treatment ice-water test and the change in urodynamic parameters after injection of botulinum toxin A, we could identify some trends. The more positive the bladder cooling reflex is, the larger increase in MCC and RV and the larger decrease in MVP can be expected after the injection. Since there is some evidence to show that both afferent and efferent effects are involved in the mechanism of action of botulinum toxin on the detrusor [19, 20] the lacking of clear positive correlations between the ice-water test criteria and the calculated quotients of the cystometric data before and after botulinum toxin can possibly be explained. We cannot interpret the negative correlation for the change in BC as it is probably related to the difficulty in calculation in small capacity bladders.

Conclusions

In the past years botulinum toxin A injections into the detrusor were shown to be a useful therapy in patients with neurogenic incontinence. Like the previous studies we could also find a significant subjective and objective improvement in our patient group. The ice-water test represents an important diagnostic tool in urodynamic assess-

ment of neurogenic bladder dysfunction. To predict the effect of the intradetrusal botulinum toxin A injection in patients with neurogenic detrusor overactivity, it can not be recommended until now based on the results of our study with 22 patients. Further studies with a larger patient group are required to evaluate the importance of the bladder-cooling test as a predictor for therapeutic options.

Conflict of interest Professor Schurch has a consultant agreement with Allergan, Irvine, CA, USA.

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